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(54) Title: NOVEL USE

(57) Abstract: A method for the treatment or prophylaxis of the common cold, or respiratory viral infection caused by human rhinovirus infection (HRV), other enteroviruses, coronavirus, influenza virus, parainfluenza virus, respiratory syncytial virus, or adenovirus infection in a human in need thereof, which method comprises administering to said human an effective amount of an NK3 antagonist.

B21

NOVEL USE

Field of Invention

The present invention relates to a novel use, in particular to the use of an NK3 antagonist alone or in combination, in the treatment of a neurogenic inflammation-mediated disease following respiratory infection.

Background of the Invention

Human rhinovirus (HRV), the most frequent cause of the common cold, is increasingly associated with more serious sequelae including exacerbations of asthma, chronic bronchitis, COPD, otitis media, and sinusitis (*Gern et. al,* Clin Micro Reviews 12(1): 9-18 (*1999*); *Pitkaranta, and Hayden,* Annals of Medicine 30 (6): 529-537 (*1998*); *Seemungal et. al,* Eur. Resp. J., 16:677-683 (*2000*)). Recent published studies in adults and adolescents, using PCR to assist in viral detection, have shown that up to 50 to 80% of asthma exacerbations are associated with upper respiratory tract virus infection, and that rhinovirus is the most common virus (*Atmar et. al,* Archives of Internal Medicine. 158 (22): 2453-9 (*1998*); *Johnston, SL.*, British Medical Journal 310: 1225-9 (*1995*)). HRV infects nasal epithelial cells. Recent evidence suggests the virus may also infect bronchial epithelium. Prodromal cold symptoms are apparent within 24 hours post-infection, peak on days 2 through 5, and resolve within seven to fourteen days, but can be more protracted in some individuals. Symptoms are believed to arise more from the host's response to infection, than an acute cytotoxic effect, since only a small fraction of upper respiratory epithelial cells are demonstrably infected, and there is minimal epithelial cell damage (*Winther et. al,* JAMA 256: 1763-1767 (*1986*)). Increased intranasal levels of kinins, IL-1, IL-8, IL-6, IL-11, and neutrophils are found in normal individuals infected with rhinoviruses. A correlation between IL-8 concentration in nasal secretions with local myeloperoxidase levels and with symptom severity has been demonstrated in several recent studies (*Grieff, et. al,* Eur Respir J 13: 41-47 (*1999*); *Teren, et. al,* Am J Respir Crit Care Med 155: 1362-1366 (*1997*), *Turner, et. al,* Clin Infect Dis 26: 840-846 (*1998*)). Intranasal concentrations of IL-1 and IL-6 have been correlated with symptom severity as well (*Proud et. al,* J. Infect. Dis.169:1007-1013 (*1994*); *Zhu et. al,* J. Clin. Invest. 97:421-430 (*1996*)). Experimental rhinovirus infection also results in enhanced immediate and late phase allergic reactions, and in increased infiltration of T lymphocytes and eosinophils into the lower airways. In atopics and asthmatics, these effects persist for up to 2 months post - infection (*Gern and Busse,* Am J Respir Crit Care Med, 152: S40-S45 (*1995*). In addition, IL-1, IL-6, and IL-8 are also produced in response to infection with other

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the treatment of viral induced inflammatory diseases with a neurogenic component or viral diseases with a significant inflammatory component or direct or indirect inflammation due to viral infection.

Summary of the Invention

The present invention relates to the use of an NK3 antagonist for the treatment, including prophylaxis, of the common cold, or respiratory infection caused by human rhinovirus infection (HRV), other enteroviruses, coronavirus, influenza virus, parainfluenza virus, respiratory syncytial virus, adenovirus or intracellular pathogens such as *chlamydia pneumoniae* infection in a human in need thereof, which method comprises administering to said human an effective amount of an NK3 antagonist.

The present invention also relates to the use of the NK3 antagonist inhibitor for the treatment, including prophylaxis, of inflammation associated with a respiratory infection of a human rhinovirus (HRV), other enteroviruses, coronavirus, influenza virus, parainfluenza virus, respiratory syncytial virus, adenovirus or other respiratory pathogens.

Brief Description of the Drawings:

Figure 1. demonstrates the effect of Compound (I) administered in the diet on RSV-induced weight loss.

Figure 2 demonstrates lung virus titers following treatment with normal rodent chow or diet containing Compound (I). Lungs were harvested at varying times post-infection, and viral load was determined by titration assay.

Figure 3 demonstrates the lack of effect on cytokines.

Detailed Description of the Invention

IL-1, TNF, and other cytokines affect a wide variety of cells and tissues and these cytokines as well as other leukocyte-derived cytokines are important and critical inflammatory mediators of a wide variety of disease states and conditions. The inhibition of these cytokines is of benefit in controlling, reducing and alleviating many of these disease states.

In particular, the present invention is directed to the treatment, including prophylaxis, of a viral infection in a human, which is caused by the human rhinovirus (HRV), other enterovirus, coronavirus, influenza virus, parainfluenza virus, respiratory syncytial virus, or an adenovirus. In particular the invention is directed to respiratory viral infections that exacerbate asthma (induced by such

infections), chronic bronchitis, chronic obstructive pulmonary disease, otitis media, and sinusitis.

It should be noted that the respiratory viral infection treated herein may also be associated with a secondary bacterial infection, such as otitis media, sinusitis, or pneumonia.

As used herein, the term "treatment" may include prophylaxis for use in a treatment group susceptible to such infections. It may also include reducing the symptoms of, ameliorating the symptoms of, reducing the severity of, reducing the incidence of, or any other change in the condition of the patient, which improves the therapeutic outcome.

It should be noted that the treatment herein is not directed to the elimination or treatment of the viral organism itself but is directed to treatment of the respiratory viral infection that exacerbates other diseases or symptoms of disease, such as asthma (induced by such infections), chronic bronchitis, chronic obstructive pulmonary disease, otitis media, and sinusitis.

The present invention will demonstrate that NK3 antagonists are useful in the treatment of symptoms associated with HRV, including exacerbations of underlying conditions such as asthma, COPD, sinusitis and otitis media amongst others.

A preferred virus for treatment herein is the human rhinovirus infection (HRV), or respiratory syncytial virus (RSV).

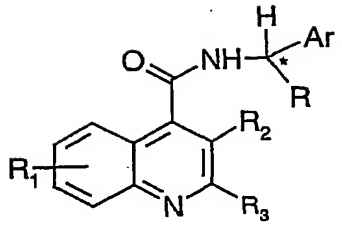
Lastly, another aspect of the present invention relates to the use of a NK3 antagonist for the treatment, including prophylaxis, of inflammation associated with a viral infection of a human rhinovirus (HRV), other enteroviruses, coronavirus, influenza virus, parainfluenza virus, respiratory syncytial virus, or adenovirus. Preferably the viral infection is HRV or RSV, or the influenza or parainfluenza virus.

Suitable NK3 antagonists include the specific examples disclosed in WO 95/32948 and WO 97/21680, especially Compound (I).

An assay for determining NK3 inhibition is also readily available using assays disclosed in the below-noted patents or applications. For instance, see U.S. Patent 5,811,553 whose disclosure is incorporated herein by reference in its entirety.

Preferred compounds of this invention include those contained in WO 97/21680, and a representative genus is described below.

Particular compounds are represented by the formula (I):



(I)

or a solvate thereof, or a salt thereof, wherein, Ar is an optionally substituted aryl or a C_{5-7} cycloalkdienyl group, or an optionally substituted single or fused ring aromatic heterocyclic group;

R is C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, optionally substituted phenyl or phenyl C_{1-6} alkyl, an optionally substituted five-membered heteroaromatic ring comprising up to four heteroatoms selected from O and N, hydroxy C_{1-6} alkyl, amino C_{1-6} alkyl, C_{1-6} alkylaminoalkyl, di C_{1-6} alkylaminoalkyl, C_{1-6} acylaminoalkyl, C_{1-6} alkoxyalkyl, C_{1-6} alkylcarbonyl, carboxy, C_{1-6} alkoxyxcarbonyl, C_{1-6} alkoxycarbonyl C_{1-6} alkyl, aminocarbonyl, C_{1-6} alkylaminocarbonyl, di C_{1-6} alkylaminocarbonyl, halogeno C_{1-6} alkyl; or R is a group $-(CH_2)_p-$ wherein p is 2 or 3 which group forms a ring with a carbon atom of Ar;

R_1 represents hydrogen or up to four optional substituents selected from the list consisting of C_{1-6} alkyl, C_{1-6} alkenyl, aryl, C_{1-6} alkoxy, hydroxy, halogen, nitro, cyano, carboxy, carboxamido, sulphonamido, C_{1-6} alkoxycarbonyl, trifluoromethyl, acyloxy, phthalimido, amino or mono- and di-C_{1-6} alkylamino;

R_2 represents a moiety $-O-(CH_2)_n-X$ wherein X is alkyl optionally substituted with one or two groups selected from hydroxy and amino; carboxy, cyano, C_{1-6} alkoxycarbonyl, aminocarbonyl, mono- or di-C_{1-6} alkylaminocarbonyl, amino-C_{1-6}-alkylaminocarbonyl or mono- or di-C_{1-6}-alkylamino-C_{1-6}-alkylaminocarbonyl; or X is a group $-NX_1X_2$ wherein X_1 and X_2 each independently represent hydrogen, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, aryl-C_{1-6}-alkylcarbonyl, heteroaryl C_{1-6}-alkylcarbonyl, aminocarbonyl, mono- or bis-C_{1-6} alkylaminocarbonyl, amino C_{1-6} alkylcarbonyl, mono-or bis-C_{1-6} alkylamino C_{1-6} alkylcarbonyl, a moiety of formula $-CO-T-CO-T_1$, wherein T is a C_{1-6} alkylene or C_{2-6} alkenylene group, and T_1 is hydroxy or C_{1-6} alkoxy, or a 5 to 9 membered single or fused ring cycloalkyl group optionally comprising 1 or 2 nitrogen atoms and optionally 1 or 2 additional heteroatoms selected from O or N and wherein one or two ring atoms are optionally substituted with C_{1-6} alkyl, said ring being optionally fused to a benzene ring; wherein the above mentioned aryl and heteroaryl groups are optionally substituted with up to two groups selected from hydroxy, C_{1-6}

alkoxy, hydroxy-C_{1-6} alkyl, amino-C_{1-6}-alkyl, mono- or bis- C_{1-6}-alkylamino, mono- or bis- C_{1-6}-alkylamino-C_{1-6}-alkyl, amino-C_{1-6}-alkoxy, mono- or bis- C_{1-6}-alkylamino-C_{1-6}-alkoxy, carboxy, C-$_{1-6}$-alkylcarbonyl, C-$_{1-6}$-alkoxycarbonyl, carboxy-C_{1-6} alkyl, carboxy-C_{1-6} alkoxy and C-$_{1-6}$-alkylcarbonyl C_{1-6} alkoxy; and wherein the alkyl moiety of any heteroaryl-C_{1-6}-alkyl or aryl-C_{1-6}-alkyl group is optionally substituted with an amino, a mono-C_{1-6}-alkylamino or a bis-C_{1-6}-alkyl amino group; or X is a C-linked single or fused ring heterocyclic group, any ring being saturated or unsaturated and consisting of 5- to 6- ring atoms, said ring atoms comprising 1 or 2 nitrogen atoms and optionally 1 or 2 additional heteroatoms selected from O or N and wherein one or two ring atoms are optionally substituted with C_{1-6} alkyl, hydroxy, amino, mono- or bis- C_{1-6}-alkylamino or an oxo substituent; and n is zero or an integer in the range of from 1 to 7 providing that when X is a group $-NX_1X_2$, n is only an integer in the range of from 2 to 7 and providing that X_1 and X_2 are not simultaneously hydrogen; or R_2 represents a moiety-NH-CO-NHY wherein Y represents C_{1-6} alkyl, aryl, aryl C_{1-3} alkyl, a moiety $-(CH_2)_p-X_3$ wherein p is an integer in the range of from 1 to 4 and X_3 is carboxy, C_{1-6} alkoxycarbonyl, or a moiety -CO-NH-$(CH_2)_q$-NX_4X_5 wherein q is an integer in the range of from 2 to 4 and X_4 and X_5 each independently represent hydrogen, C_{1-6} alkyl or C_{1-6} alkylcarbonyl; and

R_3 is branched or linear C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkylalkyl, optionally substituted aryl, or an optionally substituted single or fused ring aromatic heterocyclic group.

Suitably, Ar represents phenyl

Suitably, R represents C_{1-6} alkyl, for example, methyl, ethyl, n-propyl, isopropyl, and the like.

Preferably, R is ethyl.

Preferably, R_1 represents hydrogen.

When R_2 represents a moiety $-O-(CH_2)_n-X$ wherein n is an integer in the range of from 1 to 7, such as 1, 2 and 3, suitable values of X include carboxy, C_{1-6} alkoxycarbonyl, aminocarbonyl, mono- or di- C_{1-6} alkylaminocarbonyl or X is a C-linked single or fused ring heterocyclic group as defined n relation to formula (I); preferably X is carboxy, C_{1-6} alkoxycarbonyl, for example ethoxycarbonyl, or the said C-linked single or fused ring heterocyclic group, for example pyridyl; preferably n is 1 or 3.

In one preferred aspect R_2 is a group $-O-(CH_2)_n-X$ wherein X represents carboxy or C_{1-6} alkoxycarbonyl.

In one preferred aspect R_2 is a group -O-$(CH_2)_n$-X wherein X represents a C-linked single or fused ring heterocyclic group as defined in relation to formula (I).

When R_2 represents a moiety -O-$(CH_2)_n$-X wherein n is an integer in the range of from 2 to 7, such as 2 and 3, suitable values of X include a group -NX_1X_2 wherein X_1 and X_2 each independently represent hydrogen, alkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, mono- or di-C_{1-6} alkylaminocarbonyl, a moiety of the above defined formula -CO-T-CO-T_1 or a 5- or 6- membered cycloalkyl group said group being optionally fused to a benzene ring, providing that X_1 and X_2 are not simultaneously hydrogen; preferably one of X_1 and X_2 is hydrogen and the other is selected from heteroarylcarbonyl, arylcarbonyl or a moiety of the above defined formula -CO-T-CO-T_1.

Examples of X include carboxy, cyano, ethoxycarbonyl, aminocarbonyl, dimethylaminocarbonyl, (2-indanyl)amino and benzoylamino.

One particular value of R_2 is -O-$(CH_2)_n$-X wherein n is an integer 1, 2 or 3 and X is carboxy.

One particular value of R_2 is -O-$(CH_2)_n$-X wherein n is an integer 1, 2 or 3 and X is ethoxycarbonyl.

One particular value of R_2 is -O-$(CH_2)_n$-X wherein n is an integer 1, 2 or 3 and X is pyridyl.

One particular value of R_2 is -O-$(CH_2)_n$-X wherein n is an integer 2 or 3 and X is a group -NX_1X_2 wherein X_1 is hydrogen and X_2 is a 5 to 9 membered single ring cycloalkyl group ring fused to a benzene ring, for example a 2-indanylamino group, or an N-methyl-8-azabicyclo[3.2.1]oct-3-yl group.

One particular value of R_2 is -O-$(CH_2)_n$-X wherein n is an integer 2 or 3 and X is a group -NX_1X_2 wherein X_1 is hydrogen and X_2 is amino-C_{1-6} alkylcarbonyl or mono-or bis-C_{1-6} alkylamino C_{1-6} alkylcarbonyl, for example 2-aminoacetyl.

One particular value of R_2 is -O-$(CH_2)_n$-X wherein n is an integer 2 or 3 and X is a group -NX_1X_2 wherein X_1 is hydrogen and X_2 is a moiety of formula -CO-T-CO T_1 wherein T is a C_{1-6} alkylene, for example -CH_2CH_2-and T_1 is hydroxy or C_{1-6} alkoxy , especially hydroxy.

One particular value of R_2 is -O-$(CH_2)_n$-X wherein n is an integer 2 or 3 and X is a group -NX_1X_2 wherein X_1 is hydrogen and X_2 is optionally substituted heteroarylcarbonyl, such as 2-pyrazinylcarbonyl and 3-amino-2-pyrazinylcarbonyl.

One particular value of R_2 is -O-$(CH_2)_n$-X wherein n is an integer 2 or 3 and X is a group -NX_1X_2 wherein X_1 is hydrogen and X_2 is optionally substituted aryl-C_{1-6}-alkylcarbonyl group, such as 2-(methylaminomethyl) benzylcarbonyl, 2-

(pyrrolidinomethyl)benzylcarbonyl, 2-(pyrrolidinoethoxy)benzylcarbonyl and (2-carboxy)benzylcarbonyl.

One preferred value of R_2 is -O-$(CH_2)_n$-X wherein n is an integer 2 or 3 and X is a group -NX_1X_2 wherein X_1 is hydrogen and X_2 is a moiety of the above defined formula -CO-T-CO-T_1, for example wherein T is ethylene and T_1 is OH.

One preferred value of R_2 is -O-$(CH_2)_n$-X wherein n is an integer 2 or 3 and X is a group -NX_1X_2 wherein X_1 is hydrogen and X_2 is and substituted aryl-C_{1-6}-alkylcarbonyl, for example (2-carboxy)benzylcarbonyl and (2-pyrrolidinomethyl)benzylcarbonyl.

One preferred value of R_2 is -O-$(CH_2)_n$-X wherein n is an integer 2 or 3 and X is a group -NX_1X_2 wherein X_1 is hydrogen and X_2 is heteroarylcarbonyl, for example 2-pyrazinylcarbonyl.

When R_2 represents a moiety -O-$(CH_2)_n$-X wherein n is zero, suitable values of X include carboxy, C_{1-6} alkoxycarbonyl, for example ethoxycarbonyl.

Y suitably represents aryl, for example phenyl, or a moiety -$(CH_2)_p$-X_3.

When Y is -$(CH_2)_p$-X_3 ,p is favorably an integer 1.

When Y is -$(CH_2)_p$-X_3, X_3 is suitably C_{1-6} alkoxycarbonyl, for example ethoxycarbonyl.

Preferred compounds of formula (I) are those wherein:
Ar is phenyl, R is ethyl, R_1 is hydrogen and R_2 is a moiety -O-$(CH_2)_n$-X wherein either:

n is 1, 2 or 3 and X is carboxy, C_{1-6} alkoxycarbonyl, for example ethoxycarbonyl, or the C-linked single or fused ring heterocyclic group defined in relation to formula (I), for example pyridyl; or n is 2 or 3 and X is a group -NX_1X_2 wherein X_1 is hydrogen and X_2 is moiety of the above defined formula -CO-T-CO-T_1, for example wherein T is ethylene and T_1 is OH, or X_2 is substituted aryl-C_{1-6}-alkylcarbonyl, for example (2-carboxy)benzylcarbonyl and (2-pyrrolidinomethyl)-benzylcarbonyl or heteroarylcarbonyl, for example 2-pyrazinylcarbonyl.

Particular NK-3 antagonists are those NK-3 antagonists specifically exemplified in the above-mentioned WO 95/32948 and WO 97/21680, especially Compound (I).

Methods of using the active compounds and dosage amounts are the same as those disclosed in the references cited above. See for instance, WO 95/32948 and WO 97/21680. In order to use a compound of formula (I) or a pharmaceutically acceptable salt thereof in therapy, it will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice.

For all methods of use disclosed herein (or the compounds of Formula (I) and other NK3 antagonist compounds), suitably, the daily oral dosage regimen will be from about 0.1 to about 100 mg/kg of total body weight, preferably from about 0.2 to 50 mg/kg, more preferably from about 0.5 mg to 15 mg. The daily parenteral dosage regimen about 0.1 to about 80 mg/kg of total body weight, preferably from about 0.2 to about 30 mg/kg, and more preferably from about 0.5 mg to 15 mg/kg. The daily topical dosage regimen will preferably be from 0.1 mg to 150 mg, administered one to four, preferably two or three times daily. The daily inhalation dosage regimen will preferably be from about 0.01 mg/kg to about 1 mg/kg per day.

The NK3 antagonist may also be administered with a second therapeutic agent. The second therapeutic agent may be an antiviral agent such as ribavirin, amantidine, rimantidine, Pleconaril, AG 7088 or BTA-188; it may also be an antiviral agent such as an influenza neuraminidase inhibitor, such as zamanivar (Relenza), oseltamivir (Tamiflu) or RWJ-270201; it may be an antihistamine, such as Benadryl®, chlorpheneramine and salts thereof, brompheneramine or salts thereof, and the generally accepted non-sedating antihistamines, such as loratadine (Claritin®), descarboethoxyloratadine (DCL), fexofenadine (Allegra®), and cetirizine hydrochloride (Zyrtec®) etc., a decongestant, such as phenylpropanolamine and salts thereof, pseudoephedreine or salts thereof; steroids, such as dexamethasone, prednisone, or prenisolone, etc.; various antibiotics, such as the quinolones, cephalosporins, β-lactamase inhibitors, etc.; anti-inflammatory agents, such as an NSAID, a COX-1 or COX-2 inhibitor, ASA, or indomethacin, etc. It is recognized that the above noted agents may be administered as immediate release, or as extended release dosage forms, either together with a suitable NK3 compound, or separately. The compositions may be administered sequentially, in combination with, or contemporaneously with a NK3 agent. The administration route of the second agent may also differ from that of the CSAID agent, and hence the dosing schedule may vary accordingly.

Cetirizine HCl manufacture and dosing is described in US Patent 4,525,358; fexofenadine manufacture and dosing is described in US Patent 4,524,129; U.S. Patent 5,375,693; U.S. Patent 5,578,610; U.S. Patent 5,855,912; U.S. Patent 5,932,247; and U.S. Patent 6,037,353. Loratadine and DCL manufacture and dosing are described in U.S. Patent 4,282,233; U.S. Patent 4,371,516; U.S. Patent 4,659,716; U.S. Patent 4,863,931; U.S. Patent 5,314,697; and U.S. Patent 5,595,997.

Zanamivir dosing is disclosed in U.S. Patent 4,627,432; U.S. Patent 4,778,054; U.S. Patent 4,811,731; U.S. Patent 5,035,237; U.S. Patent 5,360,817; and

U.S. Patent 5,648,379. Oseltamivir dosing is disclosed in U.S. Patent 5,763,483; U.S. Patent 5,866,601; and U.S. Patent 5,952,375.

The NK3 antagonist may be administered systemically or non-systemically, such as orally, buccally, topically (intranasal) or via inhalation (aerosol), or both topically and via inhalation. As noted above, the second therapeutic agent may be administered by any suitable means, including parenteral, suppository, etc. which means of administration is not necessarily by the same route, nor concurrent therewith.

As used herein "topically" shall include non-systemic administration. This includes the application of a compound externally to the epidermis or the buccal cavity and/or the instillation of such a compound into the ear, eye and nose.

As used herein "systemic administration" refers to oral, intravenous, intraperitoneal and intramuscular administration, subcutaneous intranasal, intrarectal, or intravaginal.

It will be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of an NK3 antagonist will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular patient being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of an NK3 antagonist given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way.

What is claimed is:

1. A method for the treatment or prophylaxis of the common cold or respiratory viral infection caused by human rhinovirus infection (HRV), other enteroviruses, coronavirus, influenza virus, parainfluenza virus, respiratory syncytial virus, or adenovirus infection in a human in need thereof, which method comprises administering to said human an effective amount of an NK3 antagonist.

2. The method of claim 1, wherein the NK3 antagonist is (S)-N-(α-ethylbenzyl)-3-(carboxymethoxy)-2-phenylquinoline-4-carboxamide hydrochloride.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/43995

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) :A61K 31/47
US CL :514/311, 312
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/311, 312

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6,124,316 A(BICHON et al.) 26 September 2000, see the entire document.	1-2

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Date of the actual completion of the international search 30 JANUARY 2002	Date of mailing of the international search report 15 MAR 2002
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